REMARKS

Claims 1-60 are currently pending, with claims 1-23 under consideration (claims 24-60 having been withdrawn by the Examiner as drawn to non-elected subject matter). Claims 1, 4, 7, 8, 11, 13, 19, and 21 are amended by the present communication. None of the subject amendments raises an issue of new matter as all are supported by the specification at, for example, paragraph [0011], and the claims as originally filed. In view of these amendments, claims 6 and 18 are canceled herein without prejudice or disclaimer. Upon entry of the present amendment, claims 1-5, 7-17, and 19-23 and will remain pending and at issue.

Priority

The Examiner asserts that the present claims are not entitled to claim the benefit of priority of provisional application Ser. No. 60/512,651 (hereinafter "the '651 provisional application"), filed October 20, 2003, and instead are only entitled to claim the benefit of International Application No. PCT/US04/34534, filed on October 20, 2004. Applicants respectfully disagree.

In particular, the Examiner asserts that the provisional application discloses only hedgehog inhibitors and does not specifically mention agonists and antagonists. Applicants respectfully direct the Examiner's attention to pages 12-16 of the '651 provisional application. These pages are essentially identical to Watkins *et al.* (*Nature* 422:313-317, 2003), which the Examiner has cited in a rejection of claims 1-7 and 13-19 under 35 U.S.C. §102(b). Applicants respectfully submit that the Examiner's assertion that the claims are anticipated by this reference is an acknowledgment that these claims are supported by the '651 provisional application, which includes the disclosure of Watkins *et al.* in its entirety. Accordingly, Applicants further submit that, at a minimum, claims 1-7 and 13-19 are entitled to benefit of priority to the filing date of the provisional application.

Objection to the Claims

Claim 4 has been objected to based on containing an alleged informality. In particular, the Examiner indicates that the word "patway" should be replaced with "pathway." This apparent typographical error has been corrected by the present amendments to the claims, thus obviating this basis for of objection. Accordingly, reconsideration and withdrawal of this objection are respectfully requested.

Rejection under 35 U.S.C. §112, 2nd paragraph

Claims 11 and 21 stand rejected under 35 U.S.C. §112, second paragraph for allegedly being indefinite. The rejection as applied to the pending claims is respectfully traversed. Specifically, the Examiner asserts that it is unclear what the antibody or binding fragment thereof are meant to bind. Applicants, without acquiescence, have amended claims 11 and 21 to indicate that the antibody or binding fragment thereof is a hedgehog signaling pathway antagonist. As such, the skilled artisan would recognize that the antibody or binding fragment thereof would bind a component of this well-known signaling pathway and thereby block signal transduction.

Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Rejections Under 35 U.S.C. §102

Claims 1-7 and 13-19 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Watkins *et al.* (*Nature* 422:313-317, 2003; hereinafter "Watkins") as evidenced by Zhang *et al.* (*Bioorganic Med Chem Lett* 18:1359, 2008; hereinafter "Zhang"). Applicants respectfully traverse this basis for rejection.

The Examiner asserts that Watkins discloses the use of the steroid alkaloid cyclopamine and KAAD-cyclopamine to inhibit the hedgehog signaling pathway in small cell lung cancer, citing Zhang as evidence that the structure of cyclopamine reads on Applicants' invention.

Applicants submit that Watkins is not available as prior art under 35 U.S.C. §102(b). As discussed above, the present claims are entitled to claim the benefit of priority of the '651 provisional application, filed October 20, 2003. Watkins, which cites a publication date of

March 2003, was published less than a year before the priority date. Thus, Watkins fails to meet the standard under 35 U.S.C. §102(b), in which the reference must have been published more than one year prior to the date of the application. Accordingly, Watkins is not available as prior art under 35 U.S.C. §102(b).

Applicants further submit that Watkins is also not available as prior art under 35 U.S.C. §102(a). According to M.P.E.P. § 715.01(c), where the Applicant is one of the co-authors of a publication cited against his or her application, he or she may overcome the rejection by filing a specific affidavit or declaration under 37 C.F.R. § 1.132 establishing that the article is describing Applicant's own work. An affidavit or declaration by Applicant alone, indicating that Applicant is the sole inventor and that the others were merely working under his or her direction, is sufficient to remove the publication as a reference under 35 U.S.C. § 102(a). *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982).

Applicants submit herewith a declaration under 37 C.F.R. § 1.132 by Dr. Philip A. Beachy establishing that Watkins describes the inventors' own work, and indicating that Scott G. Burkholder and Baolin Wang are not inventors in the subject application. Therefore, Watkins is not available as prior art under 35 U.S.C. § 102(a) against the subject application. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-10, 13-20, and 23 stand rejected under 35 U.S.C. §102(b), as allegedly being anticipated by Lamb *et al.*, International Patent Application Publication No. WO02/080952 (hereinafter "Lamb"). Applicants respectfully traverse the rejection as it applies to the pending claims.

The Examiner asserts that Lamb teaches the use of a modulator of a hedgehog signaling pathway in the treatment of T-cell mediated diseases in which the modulator may be an inhibitor/antagonist, including cyclopamine, and the disease may be small cell lung cancer. However, contrary to the allegation set forth in the Action, Lamb does not teach all of the elements of the presently amended claims.

For example, claim 1 as currently amended is directed to a method of reducing or inhibiting proliferation or metastasis of small-cell lung cancer (SCLC) cells by contacting the SCLC cells with at least one Hh pathway antagonist. This method is based, in part, on the inventors' discovery that "Hedgehog (Hh) pathway activity dramatically increases invasiveness of SCLC cancer cells and promotes changes in expression of genes known to modulate metastasis" (see, for example, the as-filed specification at paragraph [0044]). Indeed, the present disclosure provides evidence of the role of hedgehog signaling in SCLC cell proliferation and metastasis in the *in vitro* and *in vivo* studies provided therein. For example, NCI-H249 SCLC cells treated with cyclopamine exhibited arrest of the cell cycle and apoptosis (see, for example, the as-filed specification at paragraph [0103]). In a study of malignant behavior, NCE-H249 SCLC cells treated with cyclopamine showed reduced soft agar clonogenicity, which is an *in vitro* assay of tumorigenicity (see, for example, the as-filed specification at paragraph [0104]). *In vivo* studies of the effect of cyclopamine on SCLC tumors were conducted using mice bearing SCLC xenografts. Cyclopamine-induced growth inhibition was observed for xenografts of three SCLC lines (NCI-H249, NCI-H417, and NCI-H1618, whereas no effect was observed for xenografts of A549 NSCLC cells or HCT-116 colon cancer cells (see paragraph [0104]).

In contrast, Lamb fails to teach contacting SCLC cells with an Hh antagonist to reduce or inhibit proliferation or metastasis of SCLC cells. Indeed, Lamb provides no teaching whatsoever with regard to the direct effect of hedgehog pathway antagonists on small-cell lung cancer cells, much less any *in vitro* or *in vivo* examples of such effects. Instead, the disclosure by Lamb concerns T cell-mediated disorders, and all experimental data provided demonstrate results obtained in T cell-based assays. In fact, the disclosure contains only a *single* mention of "small-cell lung cancer," among a list of other cancers (see Lamb at p. 90, lines 4-6), and is in the context of immunotherapy for the treatment of cancers (see Lamb at p. 89, line 26 to p. 90, line 3). Thus, Lamb provides no teaching or suggestion of directly contacting SCLC cells with a Hh pathway antagonist for the purpose of reducing or inhibiting proliferation or metastasis of SCLC cells. Therefore, Lamb does not anticipate the presently claimed methods of reducing or inhibiting proliferation or metastasis of SCLC, let alone methods of ameliorating SCLC in a

subject, because Lame fails to teach each and every element of the presently amended claims. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Claims 1-6, 13-18, and 23 stand rejected under 35 U.S.C. §102(e), as allegedly being anticipated by Beachy *et al.,* International Patent Application Publication No. WO03/088970 (hereinafter "Beachy"). Applicants respectfully traverse the rejection as it applies to the pending claims.

The Examiner asserts that Beachy teaches methods and reagents for inhibiting the activation of the hedgehog signaling pathway using agents such as small molecule antagonists of hedgehog pathway activity. Applicants respectfully submit, however, that Beachy does not teach all of the elements of the presently amended claims.

The presently amended claims are directed to methods of reducing or inhibiting proliferation or metastasis of small-cell lung cancer cells characterized by elevated hedgehog pathway activity, wherein the cells are contacted with at least one Hh pathway antagonist selected from the group consisting of cyclopamine, KAAD-cyclopamine, jervine, SANT-1, SANT-2, SANT-3, and SANT-4.

Beachy is directed to hedgehog signaling pathways and molecules that modulate such pathways. However, Beachy is silent with regard to cyclopamine, KAAD-cyclopamine, jervine, SANT-1, SANT-2, SANT-3, and SANT-4. Thus, Beachy does not anticipate the presently claimed invention because it fails to teach all of the elements of the presently amended claims. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-9, 13-20, and 23 stand rejected under 35 U.S.C. §102(e), as allegedly being anticipated by Dudek *et al.,* US Patent Application Publication No. 2004/0060568 (hereinafter "Dudek"). Applicants respectfully traverse the rejection as it applies to the pending claims.

In particular, the Examiner alleges that Dudek teaches methods and reagents for the inhibition of undesired growth states that occur in cells with an active hedgehog signaling

pathway. The Examiner further alleges that Dudek teaches hedgehog pathway antagonists including antibodies and cyclopamine. Applicants respectfully disagree and submit that Dudek does not anticipate the present claims because the disclosure of Dudek does not enable the presently claimed methods.

According to the Federal Circuit, the disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research,* 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003). Applicants respectfully submit that Dudek does not enable the presently claimed methods of reducing or inhibiting proliferation or metastasis of small-cell lung cancer cells, or methods of ameliorating SCLC in a subject, using a Hh signaling pathway antagonist. Indeed, Dudek provides no teaching with regard to the direct effect of hedgehog pathway antagonists on small-cell lung cancer cells, much less any *in vitro* or *in vivo* examples of such effects.

Applicants respectfully submit that Dudek merely examines Gli1 mRNA expression in SCLC tissue samples (see, for example, Table 2 in Dudek). In addition, Dudek fails to teach that Gli1 expression in SCLCs is Hedgehog-dependent; that the level of Gli1 expression is elevated in SCLC samples compared to normal lung tissue samples; or that Hedgehog antagonists would be effective in reducing or inhibiting the proliferation or metastasis of SCLC cells. Thus, in order to practice the presently claimed invention in view of Dudek, one having ordinary skill in the art would need to provide inventive effort. For example, the skilled artisan would be required to establish the link between Hedgehog signaling, Gli1 overexpression, and SCLC cell proliferation or metastasis. In addition, the skilled artisan would be required to test various Hedgehog antagonists to identify those that are effective to reduce or inhibit the proliferation or metastasis of SCLCs, as presently claimed. Clearly, the skilled artisan would be required to put forth inventive effort, and this effort would amount to undue experimentation.

In addition, the disclosure of Dudek is directed to hedgehog signaling in lung cell development and stimulation of surfactant release, as well as certain proliferative disorders derived from different cell types. However, the skilled artisan would recognize that the behavior

of a compound in one type of cell, does not necessarily predict the behavior of that compound in another type of cell, let alone a cancer cell. Thus, Dudek provides little in the way of guidance and no working examples of a method to reduce or inhibit proliferation or metastasis of small cell lung cancer cells using a Hh pathway antagonist. Therefore, Applicants submit that one of ordinary skill in the art would require inventive effort and undue experimentation to practice the presently claimed invention in view of Dudek.

Anticipation under 35 U.S.C. §102(e) requires that the reference recite each and every element of the claims in a single document, and that the single document provide an enabling disclosure of the full scope of the claimed invention. Because Dudek fails to enable the methods of the presently claimed invention, Applicants respectfully submit that the Examiner has failed to establish anticipation under 35 U.S.C. §102 (b) over Dudek. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-6, 8-18, and 20-23 stand rejected under 35 U.S.C. §102(e), as allegedly being anticipated by Ling *et al.*, US Patent Application Publication No. 2005/0054568 (hereinafter "Ling"). The rejection is respectfully traversed as it applies to the pending claims.

In particular, the Examiner alleges that Ling teaches methods and reagents for the inhibition of undesired growth states that occur in cells with an active hedgehog signaling pathway, including small cell lung cancer. The Examiner further alleges that Ling teaches hedgehog pathway antagonists including antibodies and small molecules that read on steroidal alkaloids. Applicants respectfully disagree and submit that Ling does not anticipate the present claims because the disclosure of Ling does not enable the presently claimed methods.

In particular, Applicants respectfully submit that Ling does not provide an enabling disclosure for the present methods of reducing or inhibiting proliferation or metastasis of small-cell lung cancer cells, or methods of ameliorating SCLC in a subject, using a Hh signaling pathway antagonist. Indeed, Ling provides no teaching with regard to the direct effect of hedgehog pathway antagonists on small-cell lung cancer cells, much less any *in vitro* or *in vivo* examples of such effects.

Applicants respectfully submit that Ling provides essentially the same guidance with regard to SCLC as Dudek (see, for example, Table 2 in Example 8 of Ling). Thus, Ling merely examines Gli1 mRNA expression in SCLC tissue samples. In addition, Ling fails to teach that Gli1 expression in SCLCs is Hedgehog-dependent; that the level of Gli1 expression is elevated in SCLC samples compared to normal lung tissue samples; or that Hedgehog antagonists would be effective in reducing or inhibiting the proliferation or metastasis of SCLC cells. Thus, in order to practice the presently claimed invention in view of Ling, one having ordinary skill in the art would need to provide inventive effort. For example, the skilled artisan would be required to establish the link between Hedgehog signaling, Gli1 overexpression, and SCLC cell proliferation or metastasis. In addition, the skilled artisan would be required to test various Hedgehog antagonists to identify those that are effective to reduce or inhibit the proliferation or metastasis of SCLCs, as presently claimed. Clearly, the skilled artisan would be required to put forth inventive effort, and this effort would amount to undue experimentation.

In addition, the disclosure of Ling is directed to hedgehog signaling in angiogenesis, as well as certain proliferative disorders derived from different cell types. However, the skilled artisan would recognize that the behavior of a compound in one type of cell, does not necessarily predict the behavior of that compound in another type of cell, let alone a cancer cell. Thus, Ling provides little in the way of guidance and no working examples of a method to reduce or inhibit proliferation or metastasis of small cell lung cancer cells using a Hh pathway antagonist. Therefore, Applicants submit that one of ordinary skill in the art would require inventive effort amounting to undue experimentation, to practice the presently claimed invention in view of Ling.

Anticipation under 35 U.S.C. §102(e) requires that the reference recite each and every element of the claims in a single document, and that the single document provide an enabling disclosure of the full scope of the claimed invention. Because Ling fails to enable the methods of the claimed invention, Applicants respectfully submit that the Examiner has failed to establish anticipation under 35 U.S.C. §102 (b) over Ling. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Double-Patenting Rejection

Claims 1-7, 13-19, and 23 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 43-75 of U.S. Patent Application No. 11/338,503 (hereinafter the '503 application) is respectfully traversed.

While not acquiescing to the substantive basis for this rejection and in order to reduce the issues and expedite prosecution, a terminal disclaimer over a patent that may issue from the commonly-owned '503 application is submitted herewith. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments and the remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this case.

Please charge Deposit Account No. 07-1896 in the amount of $135.00 for a Terminal Disclaimer fee and one month extension of time fee. No additional fees are believed to be due with the present communication, however, the Commissioner is hereby authorized to charge any fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896 referencing the above-referenced attorney docket number.

Respectfully submitted,

Date: March 2, 2009

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Attachment: Declaration under 37 C.F.R. § 1.132 (Beachy)
Terminal Disclaimer over U.S. Appln. Ser. No. 11/338,503